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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/175,683	10/20/98	CHEN	L 107.637.121-

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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/175,683	Applicant(s) CHEN ET AL.	
	Examiner Richard Schnizer	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,17-21 and 23-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,17-21 and 23-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No. 16 on 10/16/00. Claims 12-16 and 22 were canceled as requested. New claims 27-47 were added. Claims 1-11, 17-21, and 23-47 are pending and under consideration in this office action.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons.

The specification and Figures contain nucleotide sequences in excess of 10 nucleotides which have not been accorded a SEQ ID NO. See page 18, lines 28-30, page 19, lines 11, 12, 29, 29, 33, and 34, and Figs. 1, 2, 6, and 11. Figs. 1, 2, and 11 contain amino acid sequences in excess of 4 amino acids which are not identified by SEQ ID NO. All nucleotide sequences which are 10 nucleotides in length or longer, and all amino acid sequences 4 amino acids and longer, must be identified with a SEQ ID NO., and must be set forth in the Sequence Listing.

Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

And:

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Technical Assistance.....703-287-0200

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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-11, 17-21, and 24-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vectors and host cells comprising either SEQ ID NO:1, SEQ ID NO:1 with N182Q and N263Q mutations, or fragments of these nucleic acids encoding antigenic polypeptides; methods of making the polypeptides encoded by these nucleic acids; and for transgenic mammals which comprise these nucleic acids in their germ line operably linked to a transcription control sequence which causes their transcription in a mammary gland of the mammal, wherein the mammal expresses in a mammary gland the polypeptides encoded by these nucleic acids, and secretes the polypeptides into milk, does not reasonably provide enablement for any other nucleic acid; for transgenic animals which do not secrete MSP-1 in their milk; or for any DNA vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention encompasses nucleic acids which are modified by the introduction of silent mutations which substitute either G or C for either A or T, or silent mutations which result in the destruction of mRNA instability motifs. The nucleic acids may encode parasite proteins, viral proteins, or bacterial proteins. Also encompassed are methods of making the nucleic acids, transgenic animals comprising the nucleic acids, and vaccines comprising the nucleic acids. The utility of the invention lies in increasing the amount of protein which is expressed from a given open reading frame. The specification teaches that codon optimization and the removal of

mRNA destabilization motifs improve the ability of a given cell system to produce mRNAs corresponding to the claimed nucleic acids.

The specification teaches two examples of the claimed invention, including SEQ ID NO:1 which encodes the merozoite surface protein (MSP-1) of *Plasmodium falciparum,* and a variant of SEQ ID NO:1 wherein codons N181 and N262 are mutated to Q codons. See page 19, lines 20-25. However, the designations N181 and N262 appear to be incorrect, as positions 181 and 262 appear to encode L residues, while positions 182 and 263 encode N residues. Examination of the mutagenic oligonucleotides suggests that positions 182 and 263 are the intended target sites.

The specification teaches transgenic mice which carrying the disclosed MSP-1 nucleic acids, and which express the encoded protein in their milk. The specification teaches no other example of any parasite nucleic acid, and no example of any viral or bacterial nucleic acid.

The utility of the invention is the effect of the silent mutations on the expression of the encoded proteins. Native MSP-1 is not readily expressed in cultured mammalian cells or in transgenic animals, whereas a codon-optimized version which also lacks AUUUA mRNA destabilization motifs is well-expressed. It is assumed in the art that the use of codons corresponding to abundant charged tRNAs results in faster translation and fewer stalled ribosomes. This makes mRNAs poorer targets for RNases, thereby stabilizing them. See Seed (US Patent 5,795,737, column 1, lines 15-24). It is also known in the art that AUUUA motifs can destabilize mRNAs depending on the presence in the cell of the appropriate destabilizing proteins which bind to these sequences. AUUUA motifs have been shown to be active when

located in either the coding region or the 3'-untranslated regions of transcripts. See Akashi et al (Blood 83(11): 3182-3187, see abstract and Fig. 1). However, as Applicant points out in Paper No. 16, Akashi also teaches that there are other factors unrelated to AUUUA sequences which play a role in mRNA destabilization. In support of this, Liebhaber (Nucleic Acids Symp. Ser. 36: 29-32, 1997) teaches that the primary, secondary, and tertiary structures of mRNAs influence their stability by determining the exposure to nucleases. However Liebhaber also notes that the specific higher order structural determinants of mRNA stability were unknown at the time the invention was filed. See abstract.

Applicant has shown that the invention can be used to successfully increase the expression of MSP-1 protein in mammalian cells. Evidence is disclosed which strongly suggests that the invention functioned to stabilize MSP-1 mRNA. For this reason, the invention should be useful in increasing the expression of proteins in situations where the primary hindrance to expression is unstable mRNA, assuming that the instability of the mRNA owes to the presence of AUUUA motifs or degradation due to slow translation. However, as discussed above, Akashi and Liebhaber teach that the factors controlling mRNA stability are not limited to the presence of AUUUA motifs and the rate of translation, and can involve secondary and tertiary structures of the message. Because the higher order structural determinants which affect mRNA stability have not been determined and remain under study, one cannot predict *a priori* what sequence changes should be made to stabilize an mRNA sequence. Rather one must examine each case individually, and determine empirically which sequences are responsible for destabilizing a given mRNA, and

which mRNAs can be stabilized by codon optimization and the destruction of AUUUA motifs. One might argue that it would not be undue experimentation to examine each mRNA individually and thereby determine empirically which sequences destabilize each message. However, as set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with degree of unpredictability of factors involved.

Emphasis added. Because the nature and identity of mRNA destabilizing sequences is highly unpredictable, and the specification fails to provide any means to predict which sequences will destabilize mRNAs, one of skill in the art would have to perform undue experimentation in order to identify and replace mRNA instability motifs, or portions of instability motifs, other than AUUUA motifs.

Claim 20 encompasses transgenic animals comprising the modified nucleic acids of the invention. The nucleic acid may encode any protein, or any protein fragment, of any parasite. The asserted utility of the claimed animals is the production of the encoded parasite proteins. The specification asserts that these proteins may be used to develop vaccines. See sentence bridging pages 1 and 2. However, the language of the claim does not require that the nucleic acids must be expressed, or that the animals must have any phenotype which distinguishes them from wild type.

Clearly, one of skill in the art would not know how to use a transgenic animal of the invention which did not express the transgene and secrete the resulting antigen in its milk, because the animal would lack any phenotypic characteristic which differentiates it from the wild type. The prior art indicates that MSP-1 or its fragments can be used as a vaccine to give partial protection against malaria. See page 1, lines 31-33. For this reason, one of skill in the art could use a transgenic animal which secretes MSP-1 or the appropriate fragments in its milk. However, the specification fails to identify any other protein, or fragment, which is sufficiently antigenic to serve as a vaccine for any disease or against any organism, and fails to assert any utility for any bacterial, viral, or parasite protein, other than MSP-1.

Claims 25 and 26 encompass DNA vaccines. The vaccine of claim 25 may encode any viral, bacterial or parasite protein, whereas the vaccine of claim 26 is limited to parasite proteins. The specification provides no working example of any DNA vaccine, and no guidance as to the appropriate expression constructs, route of administration, frequency of administration, or amount of nucleic acid to administer. As indicated in the previous paragraph, the specification provides no guidance as to which polypeptides would be sufficiently antigenic to serve as a vaccine. In Genentech Inc. v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See , e.g. , Hybritech Inc. v. Monoclonal Antibodies, Inc. , 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor

> details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of which antigens could serve as vaccines, and the conditions under which the vaccine should be used, *i.e.* administration protocols, cannot be considered minor details which can be omitted in the process of providing an enabling disclosure.

In summary, because the specification fails to teach how to identify any mRNA destabilizing motif other than an AUUUA motif, and because the prior art shows that the prediction of what sequences influence mRNA stability is highly unpredictable, one of skill in the art could not make nucleic acids in which any mRNA destabilization motifs other than AUUUA had been eliminated. The only apparent utility for producing the viral, bacterial, and parasite proteins encoded by the nucleic acids of the invention is for their use as vaccines. Because, the specification fails to teach any protein or protein fragment other than MSP-1 which is suitable as a vaccine, one of skill in the art would have to perform undue experimentation to make any useful nucleic acid of the invention other than those which encode MSP-1, or its fragments which have been shown in the prior art to serve as vaccines. Because the specification provides inadequate guidance as to how to use DNA vaccines, and no guidance as to any protein other than MSP-1 which could be used to serve as a vaccine antigen, one of skill in the art would have to perform undue experimentation to make and use any DNA vaccine of the invention. Finally, claim 20

encompasses transgenic animals which lack any phenotype to distinguish them from wild type, and one of skill in the art could not use these animals for any purpose which was specific and substantial.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-11, 17-21, 23-42, 43, and 45-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-11, 17-21, 26-42, 45, and 47 are indefinite because they recite " a preferred mammary tissue-specific codon". This phrase is not adequately defined in by the claims or the specification. Applicant argues that the specification defines a preferred codon as a codon which is used more prevalently by the cell system of choice, so it should be clear that the phrase refers to codons used more prevalently by mammary gland cells. In response, it is noted that the claims do not recite "mammary gland cells", they recite "mammary cells". For this reason they encompass all cells found in mammary tissue including adipose cells, lymphocytes, red blood cells, etc. Further, it is unclear what comparison is implied by this definition. The definition could refer to codons used more prevalently by mammary cells than by either yeast cells or bacterial cells. Because yeast and bacteria have different codon preferences, the set of codons used more

prevalently by mammary cells than bacterial cells is likely to be different than the set of codons used more prevalently than yeast cells. So, it is unclear what set of codons is intended.

Claims 23-25, 38-41, 43, and 46 are indefinite because they recite the phrase "nucleic acid of a bacterial, viral, or parasitic protein". It is unclear what is intended by the association "nucleic acid of a protein". It is suggested that the word "of" should be replaced with the word "encoding".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-11, 17-19, 23, 24, 27-29, 31-33, 35-40, and 44-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Longacre-Andre et al (WO 97/30159, published 8/21/97).

Longacre-Andre the modification of a nucleic acid encoding a 42 kd C-terminal fragment of a *Plasmodium falciparum* merozoite surface protein, MSP-1. The modifications include codon optimization to reduce AT-content. See Fig. 1, which compares the modified nucleic acid to the naturally occurring nucleic acid. Note that codon 23, encoding histidine, has been altered

to CAC from CAT. This appears to represent the incorporation of a "preferred mammary tissue-specific codon", because Applicant edited all CAC codons to CAT in the working example of the instant invention. See Fig 3A of the instnat application. Also note that this substitution destroys the only AUUUA mRNA destabilization motif in the nucleic acid, and that a variety of other substitutions have been made corresponding to those made in the edited MSP-1 nucleic acid of the instant invention. See for example, the fourth codon, encoding isoleucine, and the sixth codon, encoding glutamine. Both of these codons correspond to substitutions made by Applicant in the instant invention according to Fig. 3A. Longacre-Andre also teaches a vector comprising the nucleic acid, and cells comprising the vector. It is noted that the methods of the instant invention are directed to preparing a nucleic acid for expression in a mammalian cell, whereas the nucleic acid of Longacre-Andre is expressed in an insect cell. Absent evidence to the contrary, the nucleic acid of Longacre-Andre is considered to be expressible in a mammalian cell, particularly in view of the codon optimization which increases the GC content of the nucleic acid. Because the vector comprising the nucleic acid of Longacre-Andre is foreign to the insect cell in which the nucleic acid is expressed, the vector is considered to be transgenic relative to the insect cells. Thus Longacre-Andre anticipates the claims.

Claims 23, 24, 38, 39, 40, and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Seed et al (US Patent 5,795,737, issued 8/18/98) as evidenced by GenBank L48364, 2/28/96.

Seed teaches that codon optimization may be used to increase the expression of foreign genes in mammalian cells. See column 1, lines 8-10; and column 2 lines 7-11. More particularly, Seed teaches a synthetic viral gene encoding HIV gp 120 in which nearly all the native codons were replaced with codons most frequently used in highly expressed human genes. See column 8, lines 23-30, and Fig. 1A and 1B. Preferred codons are always those with the highest possible GC content. See column 1 lines 33-37, and Table 1, bridging columns 7 and 8. Seed does not use the phrase "mammary tissue-specific codons", however, for the amino acids A, R, N, Q, H, I, L, K, P, F, and S, Seed teaches that the most preferred codon is the same codon which Applicant chose to use most frequently, as evidenced in Fig. 3A. For this reason it is concluded that Seed teaches the use of "mammary tissue-specific codons" for these amino acids. Seed also teaches avoiding the inclusion of ATTTA sequences in synthetic genes, and the synthetic gp120 gene lacks the ATTTA sequence found in the naturally occurring gp120 gene. See column 12, lines 35-37. Also compare Fig. 1A and 1B, which contain no ATTTA sequences, with the attached sequence for HIV-1 subtype MN, GenBank Accession No.L48364, which contains an ATTTA sequence at position 243. The synthetic gp120 gene was expressed in mammalian culture systems at least 2500% greater than the native form of the gp120 gene. See column 9, lines 42-46. Thus Seed anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 17-21, 23, 24, 27-34, 38-41, and 44-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dziegiel et al (US Patent 5,231,168, issued 7/21/93), Seed et al (US Patent 5,795,737, filed 9/2/95), Akashi et al (Blood 83(11): 3182-3187, 6/1994), and Bosch et al (US Patent 5,736,131, filed 9/1/94).

Dziegiel teaches an expression vector comprising a nucleic acid encoding an antigen of *Plasmodium falciparum*. See abstract. The expression vector may be used in mammalian cells for the purpose of producing and isolating the antigen, and may be used to construct transgenic animals which express the antigen. See column 18, lines 54-65; and column 19, lines 61-63. The GC content of the nucleic acid is about 30%. See column 16, lines 40-43. Prior to use of the expression vector, the nucleic acid may be modified by silent nucleotide substitutions which favor the codon usage of the organism in which the nucleic acid will be expressed. See column 20, line 66 to column 21, line 7; and column 21, lines 36-40. The nucleic acid comprises at least two ATTTA motifs within the coding region. See bases 962-966, and bases 1896-1900. Dziegiel

does not specifically recommend reducing the AT-content of the nucleic acid, the removal of mRNA instability motifs, or the introduction mammary tissue-specific codons.

Seed teaches that codon optimization may be used to increase the expression of foreign genes in mammalian cells. See column 1, lines 8-10; and column 2 lines 7-11. Preferred codons are always those with the highest possible GC content. See lines 33-37, and Table 1, bridging columns 7 and 8. Seed does not use the phrase "mammary tissue-specific codons", however, for the amino acids A, R, N, Q, H, I, L, K, P, F, and S, Seed teaches that the most preferred codon is the same codon which Applicant chose to use most frequently, as evidenced in Fig. 3A. For this reason it is concluded that Seed teaches the "mammary tissue-specific codons" for these amino acids. Seed also teaches avoiding the inclusion of AUUUA sequences in synthetic genes. See column 12, lines 35-37.

Bosch teaches removal of mRNA instability motifs from nucleic acids which are to be expressed in heterologous hosts. Bosch also teaches that codon optimization is advisable. See column 4, lines 12-21.

Akashi teaches that the function of AUUUA mRNA destabilization motifs is not restricted by their location within the mRNA. These motifs need not be located in the 3'-untranslated region of mRNAs, and are capable of destabilizing mRNAs even when located within the coding region. See abstract, and Fig. 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the nucleotide sequence of Dziegiel by decreasing its AT-content and removing mRNA

destabilization motifs. One would have been motivated to do so because Seed teaches that, of all the codons encoding a given amino acid, the preferred codon for expression in mammalian cells is the one with the highest GC-content. One would have been motivated to remove mRNA-destabilizing motifs from the coding region of the nucleic acids because Akashi teaches that these sequences can be active in the context of the coding region, and because both Bosch and Seed suggest that mRNA-destabilizing motifs should be removed from sequences to be expressed in heterologous hosts. One would have been motivated to remove the ATTTA sequences from the coding region of Dziegiel because Akashi teaches that these sequences can destabilize mRNAs even when located within the coding region. By using the preferred codons of Seed in the construction of any synthetic gene, one would apparently inherently use what Applicant refers to as "mammary tissue-specific codons", because Seed suggests the same codons used by applicant for 14 of the 18 amino acids which have more than one codon. Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments filed 10/16/00 have been fully considered as they apply to the preceding rejection, but they are not persuasive.

Applicant argues that Dziegiel provides no motivation to consider codon optimization based on proteins expressed in mammary tissue. This is irrelevant because the claims do not require codon optimization based on proteins expressed in mammary tissue. Rather the claims

refer to the use of "a preferred mammary tissue-specific codon". This phrase is indefinite for the reasons set forth above under 35 U.S.C. 112, first paragraph rejections.

Applicant argues that there is no suggestion in Seed that naturally occurring parasitic proteins would not be expressed in mammalian cells, but does not explain why this is necessary for the purpose of the rejection. It is not required by the claims. Seed teaches that the expression of proteins can be improved by codon optimization. The codons suggested for the optimization of expression in mammalian cells appear to largely correspond with those suggested by Applicant in Fig. 3A. Dziegiel suggests that a nucleic acid encoding a specific parasite protein should be expressed in mammalian cells and that the codons should be optimized to suit the cell system. Clearly, Seed and Dziegiel could be readily combined by one of ordinary skill in the art. Applicant also notes that Seed provides no motivation to consider mammary tissue expression of proteins. This is irrelevant because mammary tissue expression of proteins is required only by claim 21. Claim 21 is not included in the rejection.

Applicant argues that while Akashi studied the effect of increasing numbers of AUUUA sequences on mRNA stability, Akashi does not study the effect of removing AUUUA sequences. It should be pointed out that studying the effect of adding an AUUUA sequence is the same thing as studying the effect of removing an AUUUA sequence. A comparison was made as to the stability of the messages as a function of the number of sequences present. The stability was found to increase as the number of AUUUA sequences decreased. Akashi is relied upon in the rejection to show that, at the time of the invention, it was known in the art that AUUUA motifs

could destabilize mRNAs even when the motif was located within the coding region. Because Seed and Bosch also teach that AUUUA motifs should be avoided when constructing nucleic acids for expression in heterologous systems, one of skill in the art clearly would have been motivated to remove them from the coding region in view of the teachings of Akashi. For example, Dziegiel would have been motivated to remove the AUUUA motifs found at bases 962-966, and bases 1896-1900 of the GLURP sequence.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday-Friday from 7:30 to 4:00 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Karen M. Hauda

KAREN M. HAUDA
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Richard Schnizer, Ph. D.